Challenges 11-17

- **What has been accomplished in these Challenges?**
  - What exactly are the methodologies that were developed?
  - Describe the newly developed methodologies for:
    - bridging scales
    - addressing sparse data
    - simulating across scales
    - addressing uncertainty quantification
- **How have these methodologies impacted each field?**
  - Have they changed the questions or approaches in the field?
  - Have new theories resulted from this work to improve the understanding of the problems in the field?
- **What still needs to be done for these challenges?**
  - Are there methods from other fields that should be applied to your field?
  - What further connections need to be made to address unmet needs?
- **What questions do you want to pose to the MSM Consortium related to these challenges?**

IMAG

Summary of Outcomes of Challenges 11-17

Challenge	David Basanta	Bruce Lee	Ching-Long Lin	Analysis based on 3 Challenge leads	# of projects
1					20
2					3
3	x		x		16
4			x		14
5					16
6					15
7					4
8	x		x		17
9	x		x		22
10					7
11	x		x	2 out of 3	6
12				None	0
13				None	0
14		x			1
15		x	x	2 out of 3	8
16		x			3
17		x			3
18	x				6

Key Words in Challenges 11-17

11. **Mechanistic** multiscale models that bridge to the **population** level to capture more clinical and biological realism for the population

12. Models that generate testable hypotheses regarding the biological underpinnings of behavioral and social phenomena and processes at the individual and **population** level

13. Models that describe mechanisms through which "outside-the-skin" factors, such as behavioral stressors, social bonding, parenting behavior, etc., can lead to "inside-the-skin" changes, such as in gene expression, the microbiome, or other factors that affect health or behavior

14. Models that provide innovative characterizations of interactions between individual-level behaviors, cognition, or affective processes and group-, market-, or **population-level** outcomes

15. Models to explore underlying **mechanisms** of individual-, community-, or **population-level** preventive or therapeutic interventions

16. Novel computational modeling approaches for big data that account for simultaneous sources of data on multiple scales; from biological and physiological measures, to social and psychological variables, and to environmental or contextual or societal level factors

17. Multiscale models that characterize the implications of individual-level risks for collective outcomes, or the implications of systemic risks for individual behaviors and outcomes

An integrative statistics-guided image-based multi-scale lung model

PI(s) of MSM U01: Ching-Long Lin
Institution(s): University of Iowa

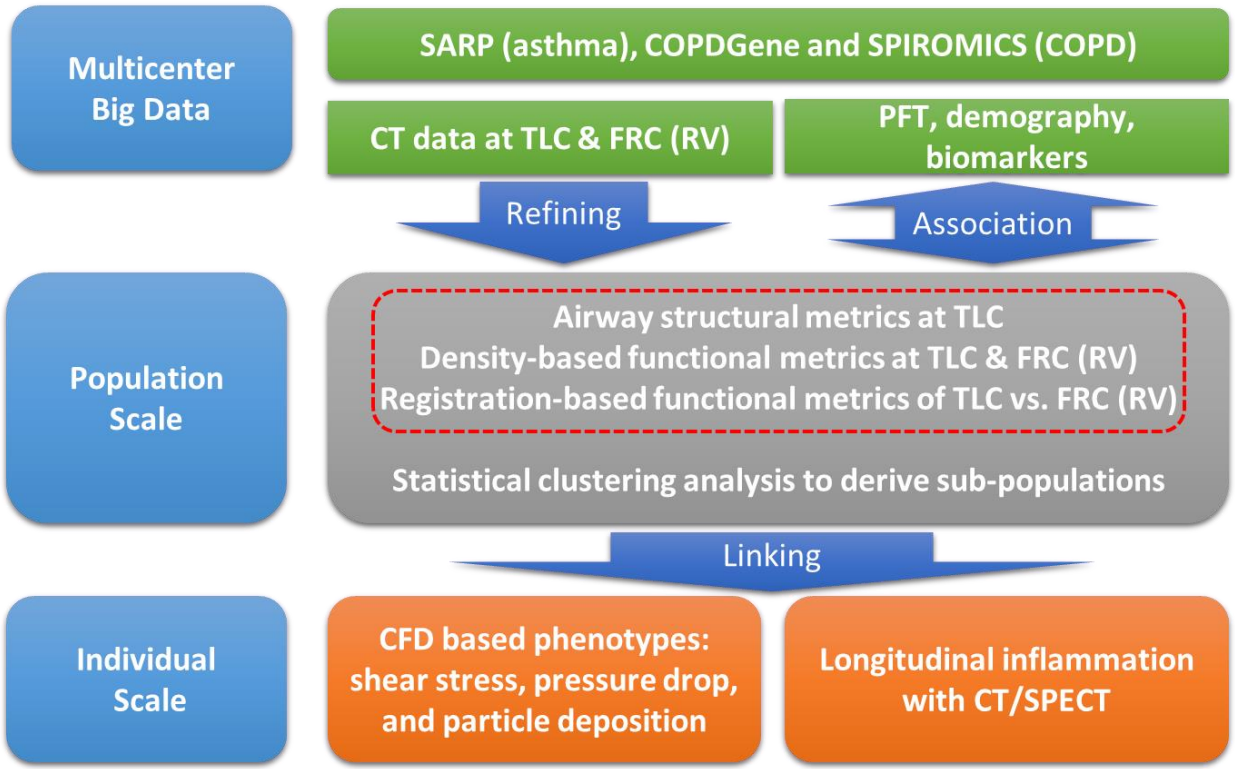
MSM U01 Grant Number: NIH U01 HL114494

- (Done) We developed a Multiscale Imaging-based Cluster Analysis (MICA) for analysis of healthy, asthma and COPD populations, allowing bridging individual and population scales. The three major challenges that we have overcome to utilize large data sets acquired by NIH-funded multi-center trials are: (1) inter-subject variability (due to, for example, gender, age and height), (2) inter-site variability (due to scanner and imaging protocol differences), and (3) definition of novel quantitative CT (QCT) imaging-based metrics at multiple scales (due to alterations at different disease stages) needed for machine/deep learning.
- (Impact) Use of the cluster membership to guide subject-specific computational fluid dynamics (CFD) analysis enables an examination of the cluster-specific structural and functional relationships toward precision medicine.
- (Future) Employment of cutting-edge deep learning techniques and development and validation of predictive models derived from MICA using longitudinal data.

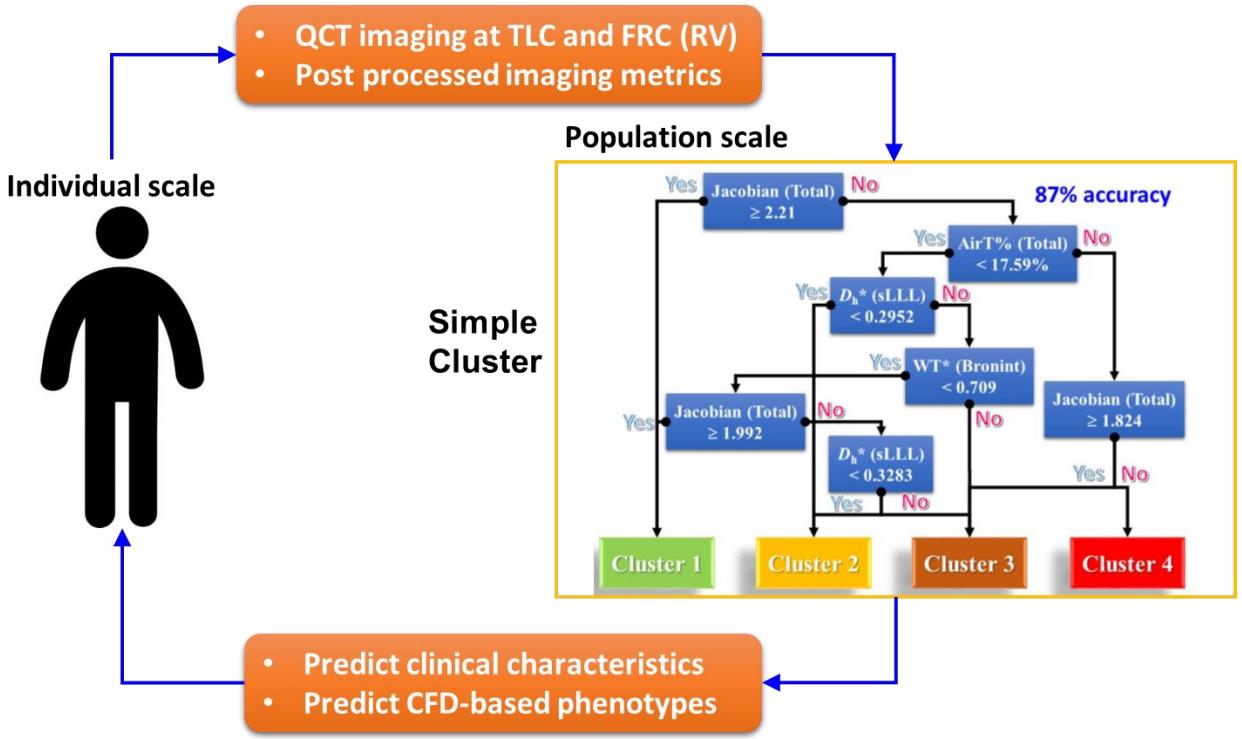
An integrative statistics-guided image-based multi-scale lung model

Engineering- Ching-Long Lin (PI), Radiology and Physiology – Eric A. Hoffman,
Bioengineering - Merryn H. Tawhai, Clinical - Alejandro Comellas, Statistics – Kung-Sik Chan

A Computational Framework



A Predictive Model Bridging Individual & Population Scales



Our multiscale imaging-based computational Fluid Dynamics (CFD) lung model can predict airflow, airway resistance and particle deposition in the human lungs.

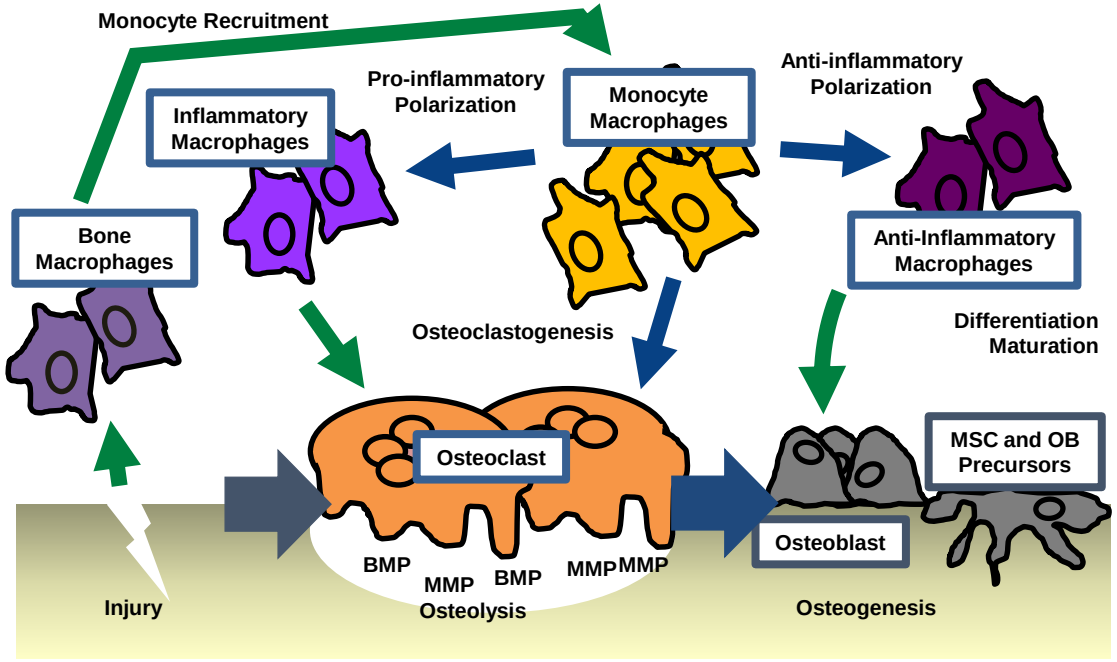
Multiscale Modeling of Bone Environment in Metastatic Prostate Cancer

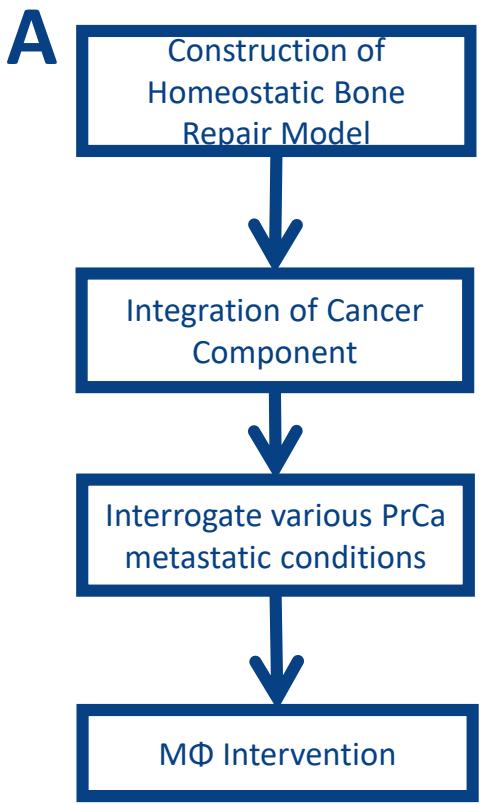
PI(s) of MSM U01: David Basanta & Conor Lynch
Institution(s): H. Lee Moffitt Cancer Center & Research Institute
MSM U01 Grant Number: 5U01CA202958

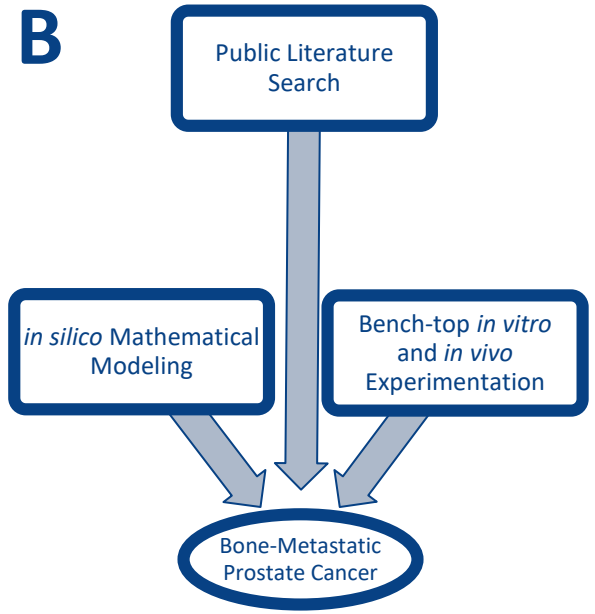
- We have developed a multiscale mathematical model that captures cellular and molecular dynamics. We have also generated a wealth of population level data from in vivo experiments where a a mouse model was used to study the role of macrophages and other myeloid-derived cells in bone repair. We are using this model to address the sparsity of single cell data by using the mathematical model to speculate different hypotheses that could explain the population/tissue level data regarding the process of repair during bone injury. By using a workflow to systematically compare different hypotheses we have compiled a comprehensive mathematical model that bridges two scales and addresses a gap in our understanding of bone biology. Bridged gaps that will allow us to understand the importance of these processes in bone metastatic cancer.
- We are proposing a systematic workflow where biological gaps can be addressed with the combination of a mathematical extensible framework and tissue-level data. Combined with our previous bottom-up approaches (where higher-scales behavior could be deduced using lower-scale biological data), we believe we can address complex previously un-addressed challenges.
- Our background in cancer modeling means that we could benefit from the expertise of researchers working on complementary models dealing with different skeletal diseases. We can also benefit from the interactions with data-driven non-mechanistic modelers with experience in clinical data.

David Basanta (Math Modeling) & Conor Lynch (Tumor Biology)
Institution: H. Lee Moffitt Cancer Center & Research Institute
Title of Grant: Multiscale Modeling of Bone Environment in Metastatic Prostate Cancer
Challenges: #11, 12, 14, 15

Integrating bench top experiments with mathematical modeling







Virtual Baltimore Lab: A Computational, Multi-Scale Model for Obesity Solutions

PI(s) of MSM U01: Bruce Y. Lee
Institution(s): Global Obesity Prevention Center at Johns Hopkins University
MSM U01 Grant Number: 121364

- We have developed VPOPs (Virtual Populations for Obesity Prevention), geospatially explicit agent based models (ABMs) of specific locations that represent scales ranging from the genetic and physiologic scale to the individual to the population and the environment to policy and economic forces. These detailed ABMs of various cities such as Baltimore and Washington, DC can serve as virtual laboratories to test different policies and interventions.
- To date, we have been working closely with different decision makers such as city government officials, retailers, and school officials to use the VPOPs to e are proposing a systematic workflow where biological gaps can be addressed with the combination of a help design and test different policies of interest such as the impact of sugar-sweetened beverage (SSB) warning labels, reducing crime, and increasing youth physical activity.
- Further develop and use such models to help design and test other policies and interventions separately and in combinations. Our interests are to connect with more and more decision makers and scientists to add more and more detail to the models.

Building multi-level models of therapeutic response in the lungs

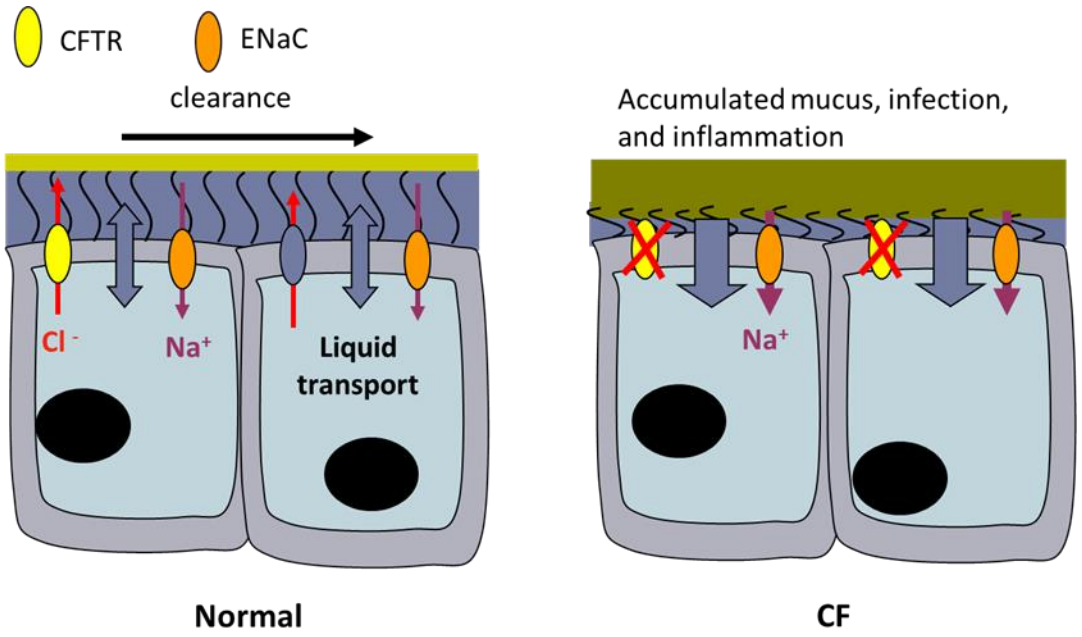
PI(s) of MSM U01: Tim Corcoran & Bob Parker
Institution(s): University of Pittsburgh
MSM U01 Grant Number: UO1 HL131046-01

- Study goal:

Create systems model that predicts organ-level and ultimately patient level therapeutic response based on in vitro studies.

- Primary disease of interest:

Cystic Fibrosis (CF) lung disease. CF is associated with defects in a single gene (CFTR) that encodes an anion channel on epithelial surfaces throughout the body. CF is associated with mucus accumulation and infection in the lungs



Why no projects address Challenges 12,13?

- Challenges #12 and #13 contain the key words of “biological underpinnings” & “gene expression” vs “behavioral” and “social”.
- There exist extra scales, viz. big gap, between them.

What questions do you want to pose to the MSM Consortium related to these challenges ?

- (CLL) Are there connections between imaging-based clusters, clinical clusters and molecular clusters shall be established?
- (DB) How can we integrate biological and clinical scales?
- (BL) Further develop and use such models to help design and test other policies and interventions separately and in combinations. Our interests are to connect with more and more decision makers and scientists to add more and more detail to the models.

What is needed to advance MSM in these areas?

- (CLL) Make existing large data sets acquired by NIH-funded multicenter trials (MCTs), e.g. the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), accessible by IMAG MSM community. Encourage collaboration between MCTs and MSM.
- (DB) Workshops integrating experimentalists, clinicians and mathematical modelers dealing with data-rich and mechanistic rich models.
- (BL) Helping more decision makers understand how such MSMs can assist with their work.